SPIRONOLACTONE IS MORE EFFECTIVE THAN EPLERENONE AT LOWERING BLOOD PRESSURE IN PATIENTS WITH PRIMARY ALDOSTERONISM

While estimates on its exact frequency vary, primary aldosteronism is a common cause of secondary hypertension and may be present in 5% to 15% of hypertensive patients. In addition to its effects on blood pressure (BP), felt mostly to be a result of increased salt and water retention, excess aldosterone levels are also associated with an increased risk of metabolic consequences, including hypokalemia and hypomagnesemia, and cardiovascular structural derangements, such as left ventricular hypertrophy (LVH) and cardiac fibrosis. The majority of patients with primary aldosteronism have bilateral idiopathic adrenal hyperplasia (IAH) requiring medical rather than surgical therapy. In these patients, effective mineralocorticoid blockade is essential for BP control. Spironolactone is the most commonly used mineralocorticoid receptor antagonist (MRA). While it has been demonstrated to effectively lower BP in patients with IAH, as its effects are not specific for the mineralocorticoid receptor, it is also frequently associated with adverse side effects. These include gynecomastia, breast tenderness, menstrual abnormalities, and impotence, which are felt to be the result of its off-target agonist activity at the progesterone receptor and its antagonist activity at the androgen receptor. The newer MRA eplerenone is a more selective inhibitor of the mineralocorticoid receptor, with up to a 500-fold lower affinity for the androgen and progestin receptors that allows it to be associated with fewer sexual side effects. As there has been only one small study directly comparing spironolactone with eplerenone in patients with hypertension associated with primary aldosteronism, the present multicenter, randomized, double-blind, noninferiority study was undertaken to compare the efficacy and tolerability of spironolactone (75–225 mg daily) with eplerenone (100–300 mg daily) in patients with IAH.

To be included in the trial, men and nonchildbearing women at least 18 years of age had to have hypertension (defined as a seated diastolic BP of at least 90 mm Hg but not >120 mm Hg and a systolic BP not >200 mm Hg), a serum potassium >3.0 and <5.0 mg/dL, the ability to discontinue current antihypertensive medication (as judged by the investigator), and evidence of primary aldosteronism. All of the following criteria had to be met to confirm the presence of primary aldosteronism: (1) serum aldosterone >20 ng/dL while consuming at least 150 mEq/d of sodium or a serum aldosterone >5 ng/dL after infusion of 2 L of isotonic saline, (2) morning plasma renin activity (PRA) <1.0 ng/mL/h after being seated for 30 minutes and off β-blocker and clonidine treatment for more than 2 weeks or an upright immunoreactive renin concentration <15 pg/mL, (3) elevated plasma aldosterone to PRA ratio >23, and (4) urine aldosterone more than 20 μg/d in the presence of urine sodium of >150 mEq/d. Radiographic evidence of IAH or results of adrenal vein sampling were considered supportive evidence of primary aldosteronism but were not required for entry in the study, as this was not a study of Conn's tumor–associated hyperaldosteronism. Exclusion criteria included systolic BP >200 mm Hg, diastolic BP >120 mm Hg, history of accelerated-malignant hypertension, planned surgical intervention for adrenal adenoma, sex hormone therapy, serum creatinine >1.5 mg/dL in men or >1.3 mg/dL in women, use of spironolactone, guanethidine or reserpine in the previous 30 days, significantly elevated transaminases >2 times the upper limit of normal, or a history of stroke, myocardial infarction, heart failure, or other serious cardiovascular event within 6 months.

Patients who met the inclusion criteria entered a 1- to 3-week pretreatment screening period followed by a 2- to 3-week single-blind, placebo run-in period. If diastolic BP rose to >120 mm Hg during this period, the run-in period was terminated early, and the patient was started on active drug therapy. After placebo run-in, patients were randomized to receive either eplerenone, starting at 100 mg daily, or spironolactone, starting at 75 mg daily. If trough seated diastolic BP remained >90 mm Hg, doses of study medication were increased at weeks 4, 8, and 12 to a maximum of 300 mg eplerenone in 100-mg increments or 225 mg spironolactone in 75-mg increments, both given once daily. The prespecified primary efficacy end point was trough seated diastolic BP at week 16. A formal test on noninferiority was conducted to establish that the treatment difference in mean diastolic BP reduction at the end of the study (spironolactone minus eplerenone) was not >4 mm Hg. There were also a number of prespecified secondary end points, including multiple different BP measurements, hormonal levels, safety and tolerability issues, and standardized quality-of-life (QOL) questionnaires. All analyses were performed using an intention-to-treat approach. All BP was measured using the Omron HEM-705CP device (Omron, Kyoto, Japan) with three readings each separated by 3 to 5 minutes taken at each measurement. The first measurement was discarded and the 2nd and 3rd were averaged for the recorded BP value. BP was measured 24 hours after the last dose of medication was taken. Plasma renin, aldosterone, and cortisol were determined at baseline and following 4, 8, and 16 weeks of treatment. In addition, sex hormone profiles (total testosterone, luteinizing hormone [LH], and total estradiol levels) were analyzed for both men and women, and 24-hour urine samples for aldosterone, potassium, sodium, creatinine, and creatinine clearance were collected at baseline and at the end of the 16-week study

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(or at early withdrawal). Finally, health-related QOL questionnaires were completed at baseline and 8 and 16 weeks postrandomization.

Overall, a total of 141 patients (71 receiving spironolactone and 70 eplerenone) were randomized to active study drug by 23 investigators. All 141 patients were included in the safety analysis, while 4 patients (2 in each group) were not included in the efficacy analysis. There were no significant differences between the groups with respect to mean age (54 years), ethnicity (88% white, 10% black), sex (66% male), or height. Mean baseline seated BP was similar in both groups (166.4/101.8 mm Hg for eplerenone and 162.6/101.8 mm Hg for spironolactone) as was serum potassium (3.48 mmol/L vs 3.34 mmol/L), plasma aldosterone (61 ng/dL vs 67 ng/dL), and other clinical parameters. Of the 68 individuals randomized to eplerenone, at week 16, three were not taking study drug, 19 were still taking 100 mg, 18 were taking 200 mg, and 28 were taking 300 mg. Of the 69 individuals randomized to spironolactone, at week 16, one was not taking therapy, 22 were taking 75 mg, 22 were taking 150 mg, and 24 were taking 225 mg.

At 16 weeks, the mean reduction in seated trough diastolic BP from baseline, the primary efficacy end point, was significantly superior in the spironolactone (−12.5 mm Hg) than the eplerenone (−5.6 mm Hg) group (change between groups, −6.9 mm Hg [95% confidence interval, −10.6 to −3.3], P=.001). Therefore, noninferiority of eplerenone was not established. Reductions from baseline in mean trough systolic BP were also significantly greater with spironolactone (−27.0 mm Hg) than with eplerenone (−9.9 mm Hg). Response rates (defined as achieved diastolic BP <90 mm Hg or a reduction in diastolic BP of 10 mm Hg from baseline) were greater with spironolactone than with eplerenone at every data collection (4, 8, 12, and 16 weeks). Additionally, at week 16, there were greater increases in PRA and plasma aldosterone in the spironolactone as compared with the eplerenone group from baseline. Small decreases in serum sodium and increases in serum potassium were seen in both groups, but these changes were greater with spironolactone. There were no significant differences between treatment groups for total testosterone and total estradiol. The adjusted mean percentage increase in LH in men was significantly greater after spironolactone treatment compared with eplerenone treatment (43.0% vs 9.0%).

In terms of tolerability, during the course of the trial far more patients taking spironolactone (63%) reported some issue with sexual function or gynecomastia than with eplerenone (37%). No significant differences, however, were found between treatment groups in overall QOL. In addition, there were no significant differences between the groups in overall incidence of treatment-emergent adverse events (76.1% with spironolactone vs 67.1% with eplerenone). In the eplerenone group, the most common reported adverse effects were headache (17.1%) and upper respiratory infection (5.7%). In the spironolactone group, the most common reported adverse effects were gynecomastia (21.2%), breast pain (21.1%), headache (21.1%), menstrual disorder (10.5%), hyperkalemia (9.9%), diarrhea (8.5%), abdominal pain (7.0%), and impotence (5.8%). In particular, gynecomastia (21.2% vs 4.5%), breast pain (21.1% vs 0%), and hyperkalemia (10.3% vs 1.5%) were significantly more common with spironolactone than with eplerenone.

In conclusion, in patients with primary aldosteronism from idiopathic bilateral adrenal hyperplasia, BP reduction using eplerenone failed the noninferiority test compared with spironolactone. At the doses studied, when given once daily, spironolactone had superior antihypertensive efficacy but a higher risk of adverse effects, than eplerenone.—*Parthasarathy HK, Menard J, White W, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spiranolactone in patients with hypertension and evidence of primary aldosteronism*. J Hypertension *2011;29:980–999*.

COMMENT

Given its effects on BP, sodium and volume, and cardiovascular structure and function, increasing attention is being paid to blocking the effects of aldosterone in patients with heart failure and hypertension, particularly resistant hypertension. It is presumed that most of the detrimental effects of aldosterone excess occur as a result of its interaction with the mineralocorticoid receptor, which is found in abundance in the heart, brain, and vasculature. Blockade of the mineralocorticoid receptor using MRAs has been demonstrated to effectively lower BP, reduce LVH, and improve clinical outcome in patients with heart failure with reduced ejection fraction.

The most commonly used MRA, spironolactone, developed in the 1950s, has been used clinically for decades. It is a relatively nonselective agent that also binds to androgen and progesterone receptors. Eplerenone is a more recently developed derivative of spironolactone designed to bind more specifically to the mineralocorticoid receptor, with up to a 500-fold lower affinity for androgen and progesterone receptors. Accordingly, as one would expect, there were far fewer complaints of gynecomastia, breast pain, and sexual dysfunction with eplerenone than with spironolactone in the present study.

While the relative binding affinities at the progesterone and androgen receptors and the difference in adverse events between these two agents are relatively well known among clinicians, less widely understood are their differences in binding affinity at the mineralocorticoid receptor and BP-lowering efficacy. In vitro, eplerenone has been reported to have a 20-fold lower binding affinity for the mineralocorticoid receptor than spironolactone. While these effects appear to be mitigated somewhat in vitro, where an approximately

50% difference in the dose required to inhibit aldosterone binding has been demonstrated, this difference is likely responsible for the large difference in BP-lowering efficacy seen between these agents in the present study.

There are also substantial pharmacokinetic and pharmacologic differences between these agents that may impact efficacy. Spironolactone undergoes fairly rapid metabolism to three active metabolites, all of which have relatively prolonged half-lives. Eplerenone also undergoes fairly rapid and comprehensive metabolism, with a half-life of about 4 to 6 hours, but, in contrast to spironolactone, its metabolites are inactive. It is therefore not surprising that eplerenone is a less-potent antihypertensive medication, especially when given once daily, as evidenced in this trial. Perhaps if higher doses of eplerenone had been used or the drug had been given twice a day, the efficacy of eplerenone would have been greater. While the maximum dose of eplerenone used in this study, 300 mg, is quite a bit higher than the 100-mg maximum dose recommended in the package insert, the drug has been tested in hypertension trials in doses up to 400 mg/d. In addition, if eplerenone was dosed twice daily instead of once a day (with blood pressure measured at trough), the efficacy of eplerenone would have been greater. Indeed, as mentioned above, the plasma half-life of eplerenone is relatively short and there are no active metabolites, so in accordance with the package insert, when BP is not controlled with 50 mg daily, it is recommended that eplerenone be increased to 50 mg twice daily (rather than 100 mg once daily).

Although the findings of this study are notable and clinically relevant, we must keep in mind that this study actually deals with a relatively narrow patient population: patients with primary aldosteronism presumed from bilateral adrenal hyperplasia who are often managed medically. While these results should not be used to preferentially choose one agent over the other for the treatment of heart failure, pending further studies it does seem reasonable, with some caveats, to extrapolate these results to the much larger patient population with primary hypertension. Both the recent scientific statement on resistant hypertension from the American Heart Association and the recent recommendations from the International Society of Hypertension in Blacks have called for increased use of MRAs in patients with difficult-to-control hypertension. The data presented in this paper, together with the known pharmacokinetics of the two agents and previous small comparison studies in primary hypertension, suggest that at least for patients with normal renal function and no evidence of baseline hyperkalemia, spironolactone should be the agent of choice when the decision is made to use an MRA. Although both agents are now generic, the price of eplerenone is still higher than the price of generic spironolactone. But even when they both become $4-a-month drugs, use of eplerenone should be reserved for patients who do not tolerate spironolactone due to gynecomastia or other sexual side effects. When eplerenone is used, it should be prescribed at approximately double the effective dose of spironolactone and used twice daily when used in doses higher than 50 mg daily. While azotemia and hyperkalemia were both exclusion criteria in the current study, both spironolactone and eplerenone can be carefully used in patients with chronic kidney disease (CKD). Eplerenone is contraindicated when creatinine clearance is <30 cc/min and spironolactone, while it has no specific level of renal function at which it is contraindicated, should be used with caution in patients with CKD. Since it has been associated with less hypokalemia in this and other trials, whether eplerenone would offer a better safety profile than spironolactone in patients with hypertension and concomitant CKD should be the subject of future investigation.

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